New Drug Application 21-825

Ferriprox® (deferiprone)

Sponsor's Proposed Indication

"for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate".

FDA Briefing Document for

The Oncologic Drugs Advisory Committee

September 14, 2011

1. Introduction

ApoPharma (a division of Apotex, Inc) has submitted a New Drug Application (NDA) for deferiprone for the treatment of patients with transfusional iron overload when current chelation therapy is inadequate. In support of its application, the sponsor has submitted data from a single, retrospective, uncontrolled, multi-institutional study (LA36-0310) entitled "Analysis of Data from Clinical Studies of Ferriprox to Evaluate its Efficacy in Patients with Iron Overload for Whom Previous Chelation Therapy Has Been Inadequate". The application also includes data from other clinical trials, some performed by the sponsor and others performed by independent investigators, as well as a number of publications related to the use of deferiprone.

This application is a resubmission of the NDA initially submitted on January 29, 2009 for the indication of "the treatment of iron overload in thalassemia patients due to transfusion therapy and for patients with transfusion dependent iron overload who had not responded to other iron chelator therapy". For that submission the sponsor provided as primary support for efficacy, data from a single, controlled trial (Study LA-16-0102). In this study, 61 adult patients with thalassemia were randomized to therapy with either deferiprone or deferoxamine. The primary efficacy measure was cardiac magnetic resonance imaging (MRI) T2* to assess cardiac iron burden. Secondary endpoints included changes in serum ferritin and liver iron concentration. Results of efficacy analyses across endpoints were inconsistent. The initial NDA submission received a Complete Response (CR) due to a number of deficiencies including the following clinical concerns: insufficiency of evidence for efficacy from adequate and well-controlled investigations; lack of sufficient information to establish the clinical meaningfulness (e.g., improved survival, symptoms, functional status or other clinical benefits) of incremental changes in cardiac MRI T2*, a major efficacy parameter in the clinical studies of deferiprone; and lack of data to verify absence of a mortality disadvantage when deferiprone is used over a long period of time. Recommendations to correct these and other deficiencies were provided to the sponsor in the CR letter. Among the recommendations was that the sponsor should provide data from at least one additional prospective, randomized, controlled clinical study that verifies the proposed deferiprone treatment effect. After further discussions with the Agency, the sponsor elected to modify the indication statement to one in which deferiprone would be used as a second line (rather than a first line) therapy. Data to support the more limited indication were to be provided from a well-documented single arm trial with prospectively specified criteria defining a patient population inadequately treated with deferoxamine (e.g., patients having a poor response with a specified persistent elevation of serum ferritin despite a specified duration of therapeutic treatment with deferoxamine). In the current resubmission the sponsor has provided a single arm trial planned to meet these criteria, Study LA36-0310. No new studies were conducted to identify patients for this study. Instead, qualified patients were identified in the sponsor's existing clinical trial database.

2. Background

Iron is essential to human existence and is a constituent of a number of proteins and enzymes in the body, predominantly hemoglobin and myoglobin. Normally iron is acquired via oral absorption from the diet in amounts that usually balance the very small quantities (1-2 mg/d) that are excreted when cells containing iron are sloughed from the skin and gastrointestinal tract. Minimal amounts are excreted in the urine. In women, iron may also be lost from blood shed at menses, and from the delivery of a child and the placenta. Otherwise, iron is tightly conserved as there are no other mechanisms available to increase the excretion of iron.

Iron overload generally occurs from either excessive gastrointestinal iron absorption or from the iron excess that accompanies repetitive red blood cell transfusions which constitute standard chronic therapy for some inherited anemias, most notably β-thalassemia. Excessive gastrointestinal absorption may occur with the inherited disorder of hemochromatosis, with excessive dietary iron and in many patients with various anemias. Many years of excessive absorption are required before any clinical consequences become apparent.

Excess iron in the body deposits in a number of sites, particularly in the liver, heart and endocrine organs. Deposition of excess iron leads to dysfunction and eventual failure of these organs.

The standard therapy for the inherited anemia, β-thalassemia, is chronic red blood cell transfusion, because these patients are unable to produce red blood cells as rapidly as they are destroyed and transfusion therapy appears to improve outcomes for both morbidity and mortality. However, each unit of packed red blood cells contains approximately 225 mg of iron. Since total body iron in the normal adult is between 3,000-5,000 mg (including all iron in circulating red cells, the liver and other reticulendothelial tissues, and in muscle), the transfusion of as little as 20 units of blood may lead to a doubling of total body iron since there are no physiologic means to increase excretion. Eventually tissue deposition of iron, hemosiderosis, develops. The main clinical complication of iron overload is cardiac hemosiderosis, which leads to congestive heart failure and arrhythmias. Before availability of chelation therapy, cardiac disease due to iron overload was responsible for about 70% of the deaths in patients with thalassemia.

Chelation therapy is based on the ability of the chelator to bind to iron in the blood or organs of deposition with the subsequent excretion of the bound complex in the urine or feces. The first drug approved for iron chelation, Desferal (deferoxamine), was approved for use in 1968 based on an understanding of its mechanism of action and uncontrolled studies that suggested its efficacy for the indication. Forty years of use has supported its efficacy and safety. However, difficulties with its administration (the need for subcutaneous or intramuscular infusion with the use of a pump over 10-12 hours 5 of 7 days each week) have limited compliance with therapy. In 2005, Exjade (deferasirox), an orally administered iron chelator, received Accelerated Approval for the treatment of

hemosiderosis due to chronic transfusion therapy for anemia in patients two years of age and older on the basis of data that showed a decrease in liver iron concentration (LIC) after treatment for one year. In clinical trials, 703 transfusion-dependent patients with underlying diagnosis of thalassemia, sickle cell disease, myelodysplastic syndrome or one of a number of miscellaneous chronic anemias were treated with deferasirox. In some of the trials, deferoxamine was used as the comparator, while other trials had no concurrent comparator. In virtually all of the trials, deferasirox showed a dose-dependent capability to reduce the mean LIC, as well as the mean serum ferritin. In a clinical trial, the administration of deferasirox to patients with values for cardiac MRI T2* in the range suggesting iron overload led to small increases in cardiac MRI T2* values after one year of treatment; however, the clinical significance of these changes has not been demonstrated. In clinical trials and in postmarketing reports, deferasirox appears to be associated with hepatic, renal, gastrointestinal, dermatological, hematological, ophthalmological, aural and hypersensitivity adverse reactions which may lead to drug discontinuation.

Patients who have transfusion related hemosiderosis and who do not respond to available iron chelators have virtually no other therapeutic options to prevent iron-induced tissue damage, particularly of the heart and liver, that eventually ends in death. Clearly an unmet medical need exists for therapies to treat patients who do not respond to marketed iron chelator therapy. The clinical benefits of iron chelator therapy on survival in patients with hemosiderosis were realized only following many years of the use of deferoxamine, the iron chelator with which we have the longest clinical experience.

Deferiprone is an oral iron chelator with the chemical name of 1,2-dimethyl-3-hydroxypyrid-4-one. Deferiprone binds iron in a 3:1 (deferiprone:iron) complex which is subsequently excreted mainly in the urine. The drug was first administered to humans in 1987 after initially being developed by independent investigators. The applicant acquired the drug in 1993 and has been responsible for its development since that date.

In 1999, deferiprone was approved in the European Union for the treatment of hemosiderosis due to transfusions in patients with thalassemia who could not be adequately treated with deferoxamine. Deferiprone is currently approved in 61 countries for this indication.

Regulatory History

Major interactions between the sponsor and the Division are summarized below.

- July 1, 1994. Original submission of the IND (IND 45724) for the use of deferiprone to treat iron overload.
- January 26, 2004. Fast track status granted for deferiprone based on potential for safe and effective use in patients who are unable to be treated with deferoxamine.
- January 29, 2009. Submission of final (Clinical/Statistical) portion of NDA.
- October 2009. Ferriprox was scheduled for presentation to the ODAC. The meeting was postponed because the Agency received additional information late in the review cycle that required time to evaluate.

- November 30, 2009. FDA issued a Complete Response letter to the NDA application to the sponsor.
- April 5, 2010. Post-Decisional Meeting. Possibility of pursuing an indication in patients who have progressive iron accumulation despite adequate deferoxamine therapy or are intolerant to deferoxamine was discussed. The requirement to clearly identify the qualified patient population (eligibility criteria) and need to specify an endpoint for accelerated approval that must be reasonably likely to predict clinical benefit were emphasized.
- April 13, 2011. Sponsor resubmitted the NDA with the revised indication and complete report for Study LA36-0310.

3. Clinical/Statistical - Efficacy

Study LA36-0310 was submitted as the major support for the indication being sought. Study LA36-0310 was designed as a retrospective analysis of existing data pooled from studies previously conducted to evaluate the efficacy and safety of deferiprone in patients with transfusion-related hemosiderosis. No new prospective clinical studies were done for this submission. The studies submitted in support of the NDA for deferiprone in the original application (and from which patients in LA36-0310 are drawn) are listed in Appendix A of this briefing document. On May 21, 2009, after submission of the original NDA, the sponsor submitted a complete study report for Study LA30-0307 entitled "A 24 Week, Open Label, Uncontrolled Study of the Safety and Efficacy of Ferriprox® (Deferiprone) Oral Solution in Iron-Overloaded Pediatric Subjects with Transfusion-Dependent Anemia". Subjects in this study also were eligible to be enrolled in Study LA36-0310.

Summary of Protocol
The primary objective of Study LA36-0310 was to evaluate the efficacy of the oral administration of deferiprone in the treatment of iron overload in patients in whom previous chelation had failed. Failure of chelation was defined by specific measures of serum iron, liver iron concentration or cardiac MRI T2* (see below).

The primary efficacy endpoint was defined as the change in serum ferritin from baseline up to completion of one year of therapy with deferiprone. Secondary endpoints were defined as the change from baseline in cardiac MRI T2* and LIC up to completion of one year of therapy.

Patients enrolled in LA36-0310 were selected from studies previously submitted to FDA in support of the original NDA. An integrated dataset including all serum ferritin, LIC, and cardiac MRI T2*, and data for demographics, disposition, medical history, exposure, and accompanied CDISC meta-tables created by Clinical Data Management at ApoPharma from these studies were sent to an independent committee (Independent Party) that was responsible for selecting patients for the analysis. Prior to receiving data from the company, the Independent Committee devised a Data Extraction Plan and Quality Control (QC) Plan which outlined the inclusion/exclusion criteria for the patient cohorts, a list of variables used to define inclusion/exclusion criteria, the logic applied to

selecting cohorts and the QC plan. The Independent Party had no access to further chelator therapy administered or to the outcomes of any of the patients treated with deferiprone.

The Independent Party consisted of two individuals:

- Ron Keren, M.D., Associate Professor of Pediatrics and Epidemiology, University of Pennsylvania School of Medicine
- Xianqun Luan, M.S., Biostatistician, Children's Hospital of Philadelphia

In the Independent Party Charter, the sponsor states that the members of the Independent Party could not have any financial, scientific or regulatory conflicts of interest, and has provided a statement to that effect signed by both members.

Patients eligible to be enrolled in the study were selected by the Independent Party based on pre-specified inclusion criteria including measurements of serum ferritin, LIC and cardiac MRI T2* and previous treatment with an iron chelator. The two Independent Party members assembled patient cohorts independently using SAS programming and by following the Data Extraction Plan and the Quality Control (QC) Plan. For each pair of cohorts, the selected patients were matched and compared for discrepancies. A QC log was issued and discrepancies were resolved before the final patient cohort lists were delivered to the sponsor. The signed QC log was delivered to the sponsor with the final selected eligible patient cohort lists. After the Independent Party provided the list of patient cohorts to the company, Clinical Data Management at the company validated the lists by performing the same SAS data runs as the Independent Party and found no discrepancies.

Patients selected by the applicant for enrollment in Study LA36-0310 from the eligible list provided by the Independent Party had to meet the following inclusion criteria:

- At least a single baseline value for serum ferritin, LIC or cardiac MRI T2* available
- Follow-up assessment of serum ferritin, LIC or MRI T2* after initiation of deferiprone and within one year of therapy
- Had been receiving standard iron chelation therapy with either deferoxamine or deferasirox and before receiving deferiprone had one or more of the following:
    - Serum ferritin > 2,500 µg/L
    - Cardiac MRI T2* < 20 ms
    - LIC > 7 mg/g dry weight
- Treatment with deferiprone [dose not specified]

Patients were excluded from enrollment for the following:

- Naïve to iron chelation therapy
- Never received deferiprone
- No data on serum ferritin, LIC or cardiac MRI T2* either while receiving standard chelation therapy or after initiation of deferiprone, or both

- Had had an improvement in any of the measures of iron burden of ≥ 20% related to another chelator therapy within the year prior to consideration for enrollment

The primary efficacy endpoint was the change in serum ferritin concentration from baseline to within one year of deferiprone therapy (defined as the observation closest to one year in a period of 15 months or at 12+3 months). For patients who stopped study treatment prior to one year, data collected up to 3 months after discontinuation was included and the value closest to the stopping date was used as the final result. Patients were considered to have been successfully treated if there was a decline in serum ferritin of at least 20% over that time period and the trial would be deemed to show evidence of efficacy if at least 20% of patients achieved the described efficacy endpoint.

Secondary endpoints included changes in the LIC and cardiac MRI T2* over the same time period.

The definition of successful chelation therapy is shown in the following table. [Note: Unless otherwise indicated, tables are from the sponsor's NDA submission].

Table 5.5.3-1: Definition of Successful Chelation Therapy

Primary endpoint	
• **Based on Serum Ferritin**	
Serum Ferritin at Baseline	**Success**
>2,500 µg/L	A ≥20% decline in serum ferritin from baseline within 1 year of Ferriprox therapy.
Secondary endpoints	
• **Based on Liver Iron Concentration (LIC)**	
LIC at baseline	**Success**
>7 mg Fe/g dw	A ≥20% decline in LIC from baseline within 1 year of Ferriprox therapy
• **Based on Cardiac Iron Concentration (as assessed by MRI T2*)**	
MRI T2* at baseline	**Success**
<20 ms	A ≥20% increase in MRI T2* from baseline within 1 year of Ferriprox therapy

dw = dry weight; LIC = liver iron concentration

The "Intent-To-Treat (ITT)" population was the primary population for the efficacy analysis. This population comprised those patients that had taken at least one dose of deferiprone and had at least one post-baseline measurement of an efficacy variable. Data were available from both randomized and non-randomized trials.

Serum ferritin was the primary efficacy endpoint, and LIC and cardiac MRI T2* were secondary endpoints. The end of study value for all endpoints was that assessment that was obtained at the end of the trial (if less than 1 year) or the value obtained at 12 months or within 3 months thereafter, utilizing the value that was closest to the 12 month date. For subjects that stopped the study early, the value closest to the stopping date was the

value used. Success was defined as noted in the table above. Success rates by study and overall and their 95% CIs were calculated based on Clopper-Pearson exact confidence interval.

The sponsor performed a number of planned and unplanned exploratory analyses. One unplanned subgroup analysis was performed by excluding patients from Studies LA-08, LA-04 and LA-12-9907 who had had concomitant or combination therapy with another chelator (mostly deferoxamine) in order to determine treatment success for monotherapy with deferiprone.

Study Results

Subject Enrollment: A total of 746 patients with serum ferritin, LIC and/or cardiac MRI T2* data were analyzed by the Independent Committee for study eligibility. Of these, 264 were deemed eligible based on the serum ferritin criterion, 117 based on the LIC criterion and 39 based on the cardiac MRI T2* criterion. These populations overlapped but were not superimposable for the three endpoints. These data are shown in the following table.

Patient Eligibility for Endpoint Assessment by Trial

	Serum Ferritin		Liver Iron Concentration		Cardiac MRI T2*	
	Total N	N for eligible patients	Total N	N for eligible patients	Total N	N for eligible patients
LA-01	35	8 (23%)	35	15 (43%)	1	0 (0%)
LA-02/06	151	65 (43%)	62	0 (0%)	1	0 (0%)
LA-03	24	8 (33%)	25	12 (48%)	--	--
LA-04/06B	157	56 (36%)	100	11 (11%)	72	10 (14%)
LA08-9701	25	7 (28%)	29	21 (72%)	--	--
LA-11	23	12 (52%)	24	3 (12.5%)	--	--
LA12-9907	69	19 (28%)	75	35 (47%)	--	--
LA15-002	29	18 (62%)	--	--	--	--
LA16-0102	29	5 (17%)	28	20 (71%)	29	29 (100%)
LA28-CMP	8	3 (38%)	2	0 (0%)	2	0 (0%)
LA30-0307	100	36 (36%)	--	--	--	--
Borgna-Pignatti	96	27 (28%)	2	0 (0%)	--	--
Total	746	264 (35%)	382	117 (30.6%)	105	39 (37%)

LIC was measured by chemical analysis of a liver biopsy or by superconducting quantum interference device (SQUID)

Reviewer table based on data from Sponsor's tables

It should be noted that the characteristics (e.g., study design, treatment duration, deferiprone doses) of the studies from which the patients for Study LA36-0310 were selected were quite varied. (See Table of Studies in Appendix A of this briefing document). For example, some studies were retrospective (LA12-9907, Borgna-Pignatti study), some studies were randomized (e.g., LA-01, LA16-0102), some studies were compassionate use (e.g., LA-03, LA-04/06B). Some patients received combination therapy with deferiprone and deferoxamine (LA08-9701).

Demographics: The demographic characteristics of the "ITT" population for the serum ferritin, LIC and cardiac MRI-T2* populations are summarized in the following table.

Demographics of the Efficacy ITT Populations

	Serum ferritin N=264	LIC N=117	MRI T2* N=39
Age (years)			
Mean ±SD	20.1 ± 12.3	19.4 ± 7.0	24.3 ± 4.7
(minimum, maximum)	(2, 76)	(6, 52)	(12, 33)
Sex: n (%)			
Female	145 (55)	55 (47)	18 (46)
Male	119 (45)	62 (53)	21 (54)
Ethnic Origin: n (%)			
Italian	138 (52)	68 (58)	14 (36)
Unknown	24 (9)	4 (3)	4 (10)
Egyptian	21 (8)	--	--
Iranian	18 (7)	--	--
Indonesian	12 (5)	--	--
Thai	12 (5)	3 (3)	--
Greek	11 (4)	21 (18)	16 (41)
Asian	6 (2)	5 (4)	1 (3)
Chinese	4 (2)	4 (3)	1 (3)
Asian Indian	3 (1)	1 (1)	2 (5)
Malay	2 (1)	--	--
Other	13 (5)	12 (12)	1 (3)
Racial Origin: n (%)			
White	194 (73)	93 (79)	31 (79)
Asian	46 (17)	21 (18)	5 (13)
Unknown	21 (8)	3 (3)	3 (8)
Other	3 (1)	--	--

Reviewer table based on data from Sponsor's tables

The population enrolled was mostly young, reflecting primarily patients with thalassemia. Only two black patients were included. Most of the patients came from outside the U.S. The demographic characteristics for the ITT populations were reasonably similar for the primary and secondary efficacy endpoints. The relatively greater proportion of Greek enrollees for the cardiac MRI T2* endpoint is accounted for by the fact that Study LA-16-0102 included only patients from one site in Greece and 2 sites in Italy.

Primary Efficacy Analysis: Change in serum ferritin was the primary efficacy endpoint. Serum ferritin was reduced by more than 20% in 136/264 patients (52%) treated with deferiprone. Based on the fact that the lower limit of the confidence interval is 45%, the sponsor indicates that it has satisfied the hypothesis premised in the study.

There was a wide variability of success (26-100%) among the various trials as shown in the following table.

Table 7.4.1-2 Success rate by study for serum ferritin – ITT population

Study	Number of patients	Success rate (N, %)	95% C.I.
LA-01	8	4 (50%)	(16%, 84%)
LA-02/06	65	26 (40%)	(28%, 53%)
LA-03	8	5 (63%)	(24%, 91%)
LA-04/06B	56	29 (52%)	(38%, 65%)
LA08-9701	7	4 (57%)	(18%, 90%)
LA-11	12	10 (83%)	(52%, 98%)
LA12-9907	19	5 (26%)	(9%, 51%)
LA15-0002	18	18 (100%)	(81%, 100%)
LA16-0102	5	4 (80%)	(28%, 99%)
LA28-CMP	3	2 (67%)	(9%, 99%)
LA30-0307	36	17 (47%)	(30%, 65%)
Borgna-Pignatti	27	12 (44%)	(25%, 65%)
Overall success rate	**264**	**136 (52%)**	**(45%, 58%)**

Source: Appendix 12.1.9.2 Statistical Appendix 4.2

Overall, the mean serum ferritin for the ITT population fell from 4416 ± 2288 µg/L to 3453 ± 2099 µg/L within one year of therapy, a mean fall of 962 µg/L (±1907).

Planned subgroup analyses were performed on several variables and all results were consistent with the results evidenced in the overall population, although persons with two or more serum ferritin determinations had higher rates of success than those with a single determination of serum ferritin, and patients outside Europe had higher rates of success than did those who were enrolled from European countries. These results are shown in the following table. Note the p-values in the sponsor's table below are not corrected for multiple analyses performed.

Table 7.4.1-6 Subgroup analysis for success rate for serum ferritin – ITT population

Subgroup	Number of patients	Success rate (N, %) (95% CI)	P-value
2 or More SF[a]	63	45 (71%) (59%, 82%)	0.0001
A Single SF	156	70 (45%) (37%, 53%)	
Paediatric Patients[b]	83	38 (46%) (35%, 57%)	0.2335
Adult Patients	181	98 (54%) (47%, 62%)	
Male	119	63 (53%) (44%, 62%)	0.7113
Female	145	73 (50%) (42%, 59%)	
Thalassemia Major	228	115 (50%) (44%, 57%)	0.4734
Non-Thalassemia Major	36	21 (58%) (41%, 74%)	
European Countries	136	54 (40%) (31%, 48%)	0.0001
Non-European Countries	128	82 (64%) (55%, 72%)	

[a]Note: among various patients for whom 2 of the 2, 2 of the 3, 3 of the 4, or 3 of the 5 serum ferritin (SF) values obtained prior to starting Ferriprox were > 2500 µg/L.
[b] Paediatric patients were <16 years of age.

An unplanned subgroup analysis was performed for subjects who received deferiprone monotherapy, as some subjects received combination chelator therapy usually combining deferiprone with deferoxamine. The success rate in this group was 50% as shown in the following table.

Table 7.4.1-5 Subgroup analysis for success rate for serum ferritin: Ferriprox Monotherapy – ITT population

Number of patients	Success rate (N, %)	95% C.I.
236	118 (50%)	(43%, 57%)

Source: Appendix 12.1.9.2 Statistical Appendix 7.7

In another unplanned exploratory analysis, the percent of patients with an initial serum ferritin of > 2500 µg/L and who experienced a decline in serum ferritin of ≥ 20% after being treated with a non-deferiprone chelator within one year were compared to patients treated with deferiprone. Success rates were 31% and 52%, respectively, as shown in the following table. Note the p-value in the sponsor's table below is not corrected for multiple analyses performed.

Table 7.4.1-7 Success rate comparison for serum ferritin between Pre-Ferriprox Group and Ferriprox Group

Group	Number of patients	Success rate (N, %) (95% CI)	P-value
Pre-Ferriprox	101	31 (31%) (22%, 41%)	0.0001
Ferriprox	264	136 (52%) (45%, 58%)	

Source: Appendix 12.1.9.2 Statistical Appendix 8.1

The trend for the mean serum ferritin showed a decline during the 12 months of the trial.

Review Comments. Deferiprone given over a period of one year was effective in lowering serum ferritin concentration in about half of the patients with transfusional hemosiderosis who had not responded adequately to available chelator therapy and whose baseline serum ferritin was > 2500 g/L. In each individual trial, at least 20% of all patients had a reduction in serum ferritin of at least 20%. The confidence intervals for the success rate in some individual studies was less than 20% (LA01, LA08, LA12 and LA28) possibly due to the small number of eligible patients in each of those studies.

Analysis of Secondary Endpoints: The change in LIC after one year of treatment with deferiprone was one of the secondary endpoints for Study LA36-0310. LIC determinations were made by either liver biopsy or by superconducting quantum interference device (SQUID). Because of the differences of LIC between the 2 methods, both the baseline and follow-up determination had to be the same in an individual subject. Of 117 subjects who had a baseline and a follow-up LIC determined and who were treated with deferiprone, 49 (42%, [C.I. 33%; 51%]) had a fall in LIC of more than 20% at the 1 year observation as shown in the following table.

Table 7.4.1-8 Overall success rate for LIC – ITT population

Study	Number of patients	Success rate (N, %)	95% C.I.
Overall	117	49 (42%)	(33%, 51%)

Source: Appendix 12.1.9.2 Statistical Appendix 5.1

The mean LIC declined from 16.2±10.3 to 14.5 ± 9.1 mg Fe/g dry weight (dw), a fall of 1.7 ± 7.5 mg Fe/ g dw over 12 months (range, -32.6 to 14.5).

The change in cardiac MRI T2* in subjects with transfusion related hemosiderosis after treatment for 1 year was an additional secondary endpoint for Study LA36-0310. Of 39 subjects who had a baseline and a follow-up cardiac MRI T2* determined and who were treated with deferiprone, 24 (62%, [C.I. 45%; 77%]) had an increase of more than 20% at 1 year of observation as shown in the following table.

Table 7.4.1-12 Success rate by study for cardiac MRI T2* – ITT population

Study	Number of patients	Success rate (N,%)	95% C.I.
LA-04/06B	10	6 (60%)	(26%, 88%)
LA16-0102	29	18 (62%)	(42%, 79%)
Overall success rate	**39**	**24 (62%)**	**(45%, 77%)**

Source: Appendix 12.1.9.2 Statistical Appendix 6.2

The mean cardiac MRI T2* rose from 11.8 ± 4.9 to 15.1 ± 7.0 ms, an increase of 3.3 ± 3.4 ms as shown in the following table. No information was provided in these patients to evaluate the relationship between change in cardiac MRI T2* and cardiac complications or clinical outcome.

Table 7.4.1-13 Descriptive statistics for cardiac MRI T2* (ms) – ITT population

	N	Mean ± SD (Minimum, Maximum)
Baseline	39	11.8 ± 4.9 (4.0, 19.5)
Last observation within 1 year + 3 months	39	15.1 ± 7.0 (3.4, 28.0)
Change	39	3.3 ± 3.4 (-2.0, 12.7)

Source: Appendix 12.1.9.2 Statistical Appendix 6.5
Note: Descriptive statistics based on log-transformed MRI T2* data were also calculated and are presented in Appendix 6.5a.

Clinical Information Relevant to Dosing Recommendations: The sponsor has not performed any significant dose-response studies. In virtually all of the trials, the total daily dose of deferiprone employed was 75 mg/kg/d divided into 3 doses taken during each day. In study LA16-0102, subjects were commenced on that dose of deferiprone and, during the next 2 months, the dose was increased in a step-wise fashion to a total daily dose of 100 mg/kg/d for the remainder of the year of the trial. In Study LA30-0307 patients were begun on deferiprone at a total daily dose of 50 mg/kg/d, but could be escalated to a maximum of 100 mg/kg/d or could have the dose reduced depending on the response in serum ferritin levels.

Discussion of Persistence of Efficacy and/or Tolerance Effects: Most of the trials performed by the sponsor had a duration of approximately 1 year. In some of the trials, subjects were allowed to continue the drug indefinitely. There is a dearth of data available to judge the continued efficacy and/or safety of deferiprone, but there have been a few patients who have remained on the drug for more than a decade. In these patients, no new safety concerns appear to have arisen.

Efficacy Summary

Based on the sponsor's analysis of the data in Study LA36-0310, the administration of deferiprone for 1 year at a dose of 75 mg/kg/d in 3 divided doses over the course of the day is capable of inducing a fall in serum ferritin from baseline to the end of 1 year of therapy by more than 20% in greater than 20% of patients who have previously been unsuccessfully treated with other approved chelating agents. An analysis based on patients who received deferiprone monotherapy demonstrated a reduction in serum ferritin by 20% in 50% (95% C.I. 43, 57%) of patients. This failure of the other chelator(s) may have been due to inability to cause a sufficient excretion of iron, imbalance between transfusion requirements and excretory capacity, development of intolerable adverse reactions to the drugs, and/or factors that compromised the patient's ability to comply with other chelator. The overwhelming majority of patients enrolled in the trial had an underlying diagnosis of thalassemia that led to the need for chronic transfusion therapy. There were too few patients with non-thalassemic syndromes enrolled in the trials to determine the efficacy of deferiprone for the treatment of transfusion-induced hemosiderosis in those populations.

Safety Summary

Since no safety data were re-analyzed in LA36-0310, the sponsor submitted an updated Safety Review which included integrated safety data from the original NDA application with all additional safety data that had been collected through August 31, 2010, plus non-integrated safety data collected between September 1, 2010 and January 31, 2011. The additional data are from ongoing trials as well as post-marketing surveillance activities.

The only additional study completed by the sponsor since August 31, 2006 was study LA30-0307, which evaluated the safety and efficacy of a deferiprone oral solution (100 mg/ml) for the treatment of hemosiderosis in transfusion-dependent pediatric thalassemia patients. The study report for LA30-0307 was submitted to IND 45724 on May 29, 2009. Patients completing this study were eligible to continue the receiving the oral solution through a Compassionate Use Protocol (LA28-CMP). The sponsor has continued to provide deferiprone to patients with transfusion-related hemosiderosis in the U.S. and Canada through its long-standing compassionate use program under study LA-04. The sponsor commenced a new study (LA35-PM) on June 6, 2010. This is a postmarketing surveillance program that seeks to evaluate the use and monitoring of deferiprone under clinical practice conditions, with assessments of both efficacy and safety.

Compared to the data submitted in the original NDA, safety data in the current submission, when re-integrated with the previous submission, shows a lower mean age (due to the fact that 100/186 new subjects in the database are children, aged 1 -10 years, who entered on to study LA30-0307). In pooled clinical studies of the re-integrated data, 642 subjects were treated with doses of deferiprone between 50 – 100 mg/kg/d. Deferiprone was co-administered with deferoxamine to an additional 89 subjects.

Durations of exposure in the pooled clinical studies at various doses are shown in the following table.

Table 2.1-1: Duration of Study Drug Exposure in Pooled Clinical Studies

	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
Subjects Exposed [N]	25	407	108	642	118	89
Subject-Years Exposure (sum)	25.9	987.1	148.5	1338.8	129.3	134.6
Mean	1.04	2.43	1.37	2.09	1.10	1.51
SD	0.59	2.32	0.78	2.13	0.74	1.43
Median	1.23	2.15	1.02	1.34	0.99	0.98
Min, Max	0.02, 1.83	0.00, 14.89	0.08, 2.54	0.00, 14.89	0.06, 2.67	0.01, 5.60
Duration of Exposure [n(%)]						
Any Exposure	25 (100.0)	407 (100.0)	108 (100.0)	642 (100.0)	118 (100.0)	89 (100.0)
>= 1 Day	25 (100.0)	407 (100.0)	108 (100.0)	642 (100.0)	118 (100.0)	89 (100.0)
>= 1 Week	25 (100.0)	406 (99.8)	108 (100.0)	638 (99.4)	118 (100.0)	87 (97.8)
>= 1 Month	21 (84.0)	391 (96.1)	108 (100.0)	616 (96.0)	108 (91.5)	84 (94.4)
>= 6 Months	19 (76.0)	301 (74.0)	88 (81.5)	492 (76.6)	96 (81.4)	72 (80.9)
>= 1 Year	16 (64.0)	246 (60.4)	61 (56.5)	365 (56.9)	46 (39.0)	36 (40.4)
>= 2 Years	0 (0.0)	209 (51.4)	33 (30.6)	264 (41.1)	23 (19.5)	18 (20.2)
>= 3 Years	0 (0.0)	127 (31.2)	0 (0.0)	145 (22.6)	0 (0.0)	15 (16.9)
>= 4 Years	0 (0.0)	95 (23.3)	0 (0.0)	107 (16.7)	0 (0.0)	10 (11.2)
>= 5 Years	0 (0.0)	74 (18.2)	0 (0.0)	80 (12.5)	0 (0.0)	4 (4.5)
>= 6 Years	0 (0.0)	17 (4.2)	0 (0.0)	19 (3.0)	0 (0.0)	0 (0.0)
>= 7 Years	0 (0.0)	7 (1.7)	0 (0.0)	9 (1.4)	0 (0.0)	0 (0.0)
>= 8 Years	0 (0.0)	6 (1.5)	0 (0.0)	8 (1.2)	0 (0.0)	0 (0.0)
>= 9 Years	0 (0.0)	6 (1.5)	0 (0.0)	8 (1.2)	0 (0.0)	0 (0.0)
>= 10 Years	0 (0.0)	4 (1.0)	0 (0.0)	6 (0.9)	0 (0.0)	0 (0.0)
>= 11 Years	0 (0.0)	3 (0.7)	0 (0.0)	5 (0.8)	0 (0.0)	0 (0.0)
>= 12 Years	0 (0.0)	3 (0.7)	0 (0.0)	5 (0.8)	0 (0.0)	0 (0.0)
>= 13 Years	0 (0.0)	3 (0.7)	0 (0.0)	5 (0.8)	0 (0.0)	0 (0.0)
>= 14 Years	0 (0.0)	3 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
3) There are 13 subjects, whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These subjects are included in Ferriprox (all doses) and were exposed for a total of 42.6 subject-years.
4) Duration of Exposure (days) is calculated as ((End Date of Exposure - Start Date of Exposure +1) - sum of interruption days), 1 month is taken to be equivalent to 30.5 days.
5) Data cutoff date: 31Aug2010

Based on sales data, the sponsor estimates that there have been 33,725 patient-years of exposure to deferiprone tablets and 318 patient-years of exposure to deferiprone oral solution worldwide.

Reviewer Comments. The sponsor has not adequately studied multiple doses of deferiprone to determine the optimal dose usage for varying body iron burdens. The majority of patients (407/642, 63.4%) were treated with a daily dose of 75 mg/kg/d and it is primarily in that group that the duration of therapy was equal to or had exceeded 1 year. Only 88 patients were treated at a dose of 100 mg/kg/d for a duration of more than 6 months, 61 were treated for more than 1 year, 33 were treated for more than 2 years and

none was treated with that dose for more than 3 years. Therefore, evidence for the efficacy and safety of doses of deferiprone greater than 75 mg/kg/d for the required time of treatment for likely recipients of the drug is limited.

The demographic characteristics of the patients treated with deferiprone in clinical trials are shown in the next table.

Table 3.1-1: Combined Demographic Profile in Pooled Clinical Studies

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
Age (Years)						
N	25	407	108	642	118	89
Mean	33.2	20.7	14.7	20.7	20.4	24.3
SD	12.1	13.2	12.7	13.3	6.8	9.5
Median	32.0	18.0	8.5	19.0	20.0	23.0
Min, Max	5, 62	1, 77	1, 70	1, 77	6, 35	10, 54
Age [n(%)]						
1 - 5 Years	1 (4.0)	25 (6.1)	33 (30.6)	61 (9.5)	0 (0.0)	0 (0.0)
6 - 11 Years	0 (0.0)	40 (9.8)	31 (28.7)	81 (12.6)	15 (12.7)	6 (6.7)
12 - 15 Years	0 (0.0)	72 (17.7)	0 (0.0)	80 (12.5)	16 (13.6)	7 (7.9)
16 - 17 Years	2 (8.0)	44 (10.8)	0 (0.0)	51 (7.9)	10 (8.5)	4 (4.5)
>= 18 Years	22 (88.0)	226 (55.5)	44 (40.7)	369 (57.5)	77 (65.3)	72 (80.9)
Sex [n(%)]						
Male	17 (68.0)	197 (48.4)	57 (52.8)	320 (49.8)	56 (47.5)	44 (49.4)
Female	8 (32.0)	210 (51.6)	51 (47.2)	322 (50.2)	62 (52.5)	45 (50.6)
Race [n(%)]						
White	1 (4.0)	333 (81.8)	71 (65.7)	457 (71.2)	103 (87.3)	50 (56.2)
Black	0 (0.0)	3 (0.7)	0 (0.0)	4 (0.6)	1 (0.8)	1 (1.1)
Asian	24 (96.0)	34 (8.4)	33 (30.6)	114 (17.8)	14 (11.9)	14 (15.7)
Unknown	0 (0.0)	36 (8.8)	2 (1.9)	59 (9.2)	0 (0.0)	20 (22.5)
Multi-Racial	0 (0.0)	1 (0.2)	2 (1.9)	8 (1.2)	0 (0.0)	4 (4.5)

1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
3) There are 13 subjects, whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day.
4) The Age when subjects were first exposed to Ferriprox is used.
5) Out of 642 subjects 222 were pediatric (< 16 years old) and 420 were adults (>=16 years oold).
6) Data cutoff date: 31Aug2010

Reviewer Comments. The mean age of the subjects exposed to all doses of deferiprone was 20.7 years, reflecting the fact that the majority of subjects who were enrolled had a base diagnosis of thalassemia. There was a representation of pediatric patients but most of these were patients treated with the liquid oral formulation of the drug at a dose of 100 mg/kg/d. Most of the subjects were white with most of the remaining being Asians. Only 4 black subjects were included in the clinical trials. The demographic characteristics of patients in Study LA36-0310 most closely matched that of patients exposed to 75 mg/kg/day of deferoxamine.

The baseline characteristics of the patients treated with deferiprone are shown in the following table.

Table 3.2-1: Baseline Characteristics of Subjects in Pooled Clinical Studies

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
Primary Disease (Sponsor Defined) [n (%)]						
Aplasia Pure Red Cell	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Aplastic Anemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Blackfan-Diamond Anemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
Chronic Lymphocytic Leukemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Congenital Anaemia	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (2.2)
Hemoglobin E-Thalassemia Disease	24 (96.0)	1 (0.2)	9 (8.3)	42 (6.5)	0 (0.0)	5 (5.6)
Hereditary Haemochromatosis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Myelodysplasia	0 (0.0)	12 (2.9)	1 (0.9)	15 (2.3)	0 (0.0)	1 (1.1)
Myelofibrosis	0 (0.0)	4 (1.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)
Refractory Anaemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Severe Hemolytic Anemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Sickle Cell Disease	0 (0.0)	4 (1.0)	1 (0.9)	5 (0.8)	0 (0.0)	0 (0.0)
Thalassemia Intermedia	0 (0.0)	4 (1.0)	0 (0.0)	5 (0.8)	0 (0.0)	1 (1.1)
Thalassemia Major	1 (4.0)	375 (92.1)	97 (89.8)	560 (87.2)	118 (100.0)	78 (87.6)
Transfusion Dependent Aase Syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
Transfusion Dependent Refractory Anemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Baseline Splenectomy Status [n(%)]						
Positive	0 (0.0)	135 (33.2)	18 (16.7)	204 (31.8)	18 (15.3)	49 (55.1)
Negative	1 (4.0)	204 (50.1)	90 (83.3)	345 (53.7)	54 (45.8)	40 (44.9)
Missing Data	24 (96.0)	68 (16.7)	0 (0.0)	93 (14.5)	46 (39.0)	0 (0.0)

	Ferriprox 50 mg/kg/d n=25 (%)	Ferriprox 75 mg/kg/d n=407 (%)	Ferriprox 100 mg/kg/d n=108 (%)	Ferriprox (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with Ferriprox n=89 (%)
Baseline Hepatitis C Status [n(%)]						
Positive	0 (0.0)	208 (51.1)	30 (27.8)	258 (40.2)	52 (44.1)	17 (19.1)
Negative	1 (4.0)	175 (43.0)	64 (59.3)	279 (43.5)	66 (55.9)	36 (40.4)
Missing Data	24 (96.0)	24 (5.9)	14 (13.0)	105 (16.4)	0 (0.0)	36 (40.4)
Baseline Serum Ferritin [n(%)]						
<= 2,500 µg/L	10 (40.0)	229 (56.3)	60 (55.6)	356 (55.5)	79 (66.9)	49 (55.1)
> 2,500 µg/L	14 (56.0)	177 (43.5)	48 (44.4)	284 (44.2)	39 (33.1)	40 (44.9)
Missing Data	1 (4.0)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
Baseline ALT [n(%)]						
<= 2 x ULN	21 (84.0)	316 (77.6)	95 (88.0)	511 (79.6)	97 (82.2)	70 (78.7)
> 2 x ULN	4 (16.0)	90 (22.1)	13 (12.0)	130 (20.2)	21 (17.8)	19 (21.3)
Missing Data	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Baseline ANC [n(%)]						
< 1.5 x 10/L	0 (0.0)	6 (1.5)	0 (0.0)	8 (1.2)	1 (0.8)	2 (2.2)
>=1.5 x 10/L	25 (100.0)	400 (98.3)	108 (100.0)	633 (98.6)	117 (99.2)	87 (97.8)
Missing Data	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

1) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
2) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
3) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day.
4) Data cutoff date: 31Aug2010

Reviewer Comments. Thalassemia (beta or E-thalassemia) was the cause for anemia in 93.7% of patients. There was minimal representation of patients with myelodysplastic syndrome (15 patients, 2.3% of all enrollees). Patients with sickle cell disease numbered only 5 (0.8%). The baseline serum ferritin was > 2500 µg/L in 44.2% of enrolled subjects.

The current submission adds 100 subjects who received deferiprone at a dose of 100 mg/kg/d to the previous submission database. About half of these subjects were between the ages of 1 -11 years. There was no remarkable difference in the frequency or type of adverse reactions based on dose, although an increase in dose appeared to be associated with a decrease in gastrointestinal complaints, and an increase in the frequency of "neutrophils decreased" (0% at 50 mg/kg/d, 6.9% at a dose of 75 mg/kg/d and 19.4% at a dose of 100 mg/kg/d), the development of neutropenia (4.0% at a dose of 50 mg/kg/d, 7.1% at a dose of 75 mg/kg/d and 7.4% at a dose of 100 mg/kg/d), elevation of alanine aminotransferase and in body weight. These data are shown in the following table.

Table 4.1-1: Summary of On-Treatment Adverse Events in Pooled Clinical Studies Occurring in >5% Subjects

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
SUBJECTS WITH ANY AE	23 (92.0)	346 (85.0)	94 (87.0)	538 (83.8)	100 (84.7)	68 (76.4)
SUBJECTS WITH ANY AE OCCURRING IN > 5%	19 (76.0)	329 (80.8)	81 (75.0)	486 (75.7)	93 (78.8)	52 (58.4)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (4.0)	40 (9.8)	8 (7.4)	56 (8.7)	10 (8.5)	5 (5.6)
NEUTROPENIA	1 (4.0)	29 (7.1)	8 (7.4)	43 (6.7)	5 (4.2)	5 (5.6)
LYMPHADENOPATHY	0 (0.0)	11 (2.7)	0 (0.0)	13 (2.0)	6 (5.1)	0 (0.0)
GASTROINTESTINAL DISORDERS	15 (60.0)	197 (48.4)	37 (34.3)	272 (42.4)	36 (30.5)	21 (23.6)
NAUSEA	9 (36.0)	87 (21.4)	13 (12.0)	117 (18.2)	3 (2.5)	7 (7.9)
VOMITING	2 (8.0)	76 (18.7)	17 (15.7)	108 (16.8)	14 (11.9)	12 (13.5)
ABDOMINAL PAIN UPPER	0 (0.0)	64 (15.7)	11 (10.2)	79 (12.3)	10 (8.5)	2 (2.2)
ABDOMINAL PAIN	0 (0.0)	63 (15.5)	10 (9.3)	76 (11.8)	11 (9.3)	2 (2.2)
DIARRHOEA	7 (28.0)	46 (11.3)	10 (9.3)	73 (11.4)	5 (4.2)	10 (11.2)
TOOTHACHE	0 (0.0)	47 (11.5)	3 (2.8)	53 (8.3)	9 (7.6)	3 (3.4)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (12.0)	169 (41.5)	19 (17.6)	210 (32.7)	37 (31.4)	16 (18.0)
PYREXIA	3 (12.0)	147 (36.1)	14 (13.0)	181 (28.2)	15 (12.7)	15 (16.9)
FATIGUE	0 (0.0)	26 (6.4)	2 (1.9)	31 (4.8)	10 (8.5)	2 (2.2)
ASTHENIA	0 (0.0)	18 (4.4)	3 (2.8)	21 (3.3)	9 (7.6)	0 (0.0)
MALAISE	0 (0.0)	7 (1.7)	0 (0.0)	8 (1.2)	10 (8.5)	0 (0.0)
INJECTION SITE PAIN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	12 (10.2)	0 (0.0)
INFECTIONS AND INFESTATIONS	9 (36.0)	232 (57.0)	47 (43.5)	317 (49.4)	71 (60.2)	28 (31.5)

NASOPHARYNGITIS	1 (4.0)	154 (37.8)	15 (13.9)	182 (28.3)	44 (37.3)	11 (12.4)
PHARYNGITIS	0 (0.0)	113 (27.8)	26 (24.1)	149 (23.2)	23 (19.5)	10 (11.2)
INFLUENZA	0 (0.0)	120 (29.5)	1 (0.9)	127 (19.8)	15 (12.7)	6 (6.7)
TONSILLITIS	1 (4.0)	35 (8.6)	1 (0.9)	40 (6.2)	2 (1.7)	3 (3.4)
BRONCHITIS	1 (4.0)	31 (7.6)	2 (1.9)	36 (5.6)	3 (2.5)	1 (1.1)
UPPER RESPIRATORY TRACT INFECTION	8 (32.0)	14 (3.4)	6 (5.6)	35 (5.5)	7 (5.9)	6 (6.7)
EAR INFECTION	0 (0.0)	31 (7.6)	0 (0.0)	33 (5.1)	1 (0.8)	1 (1.1)
RHINITIS	0 (0.0)	17 (4.2)	11 (10.2)	30 (4.7)	6 (5.1)	2 (2.2)
PHARYNGOTONSILLITIS	0 (0.0)	20 (4.9)	0 (0.0)	23 (3.6)	6 (5.1)	3 (3.4)
VIRAL INFECTION	0 (0.0)	10 (2.5)	7 (6.5)	19 (3.0)	10 (8.5)	1 (1.1)
GASTROENTERITIS	0 (0.0)	12 (2.9)	3 (2.8)	17 (2.6)	7 (5.9)	2 (2.2)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**0 (0.0)**	**13 (3.2)**	**4 (3.7)**	**19 (3.0)**	**12 (10.2)**	**2 (2.2)**
TRANSFUSION REACTION	0 (0.0)	10 (2.5)	4 (3.7)	15 (2.3)	6 (5.1)	1 (1.1)
CONTUSION	0 (0.0)	3 (0.7)	0 (0.0)	4 (0.6)	6 (5.1)	1 (1.1)
INVESTIGATIONS	**2 (8.0)**	**110 (27.0)**	**46 (42.6)**	**174 (27.1)**	**17 (14.4)**	**13 (14.6)**
BIOPSY LIVER	0 (0.0)	66 (16.2)	0 (0.0)	70 (10.9)	1 (0.8)	2 (2.2)
NEUTROPHIL COUNT DECREASED	0 (0.0)	28 (6.9)	21 (19.4)	57 (8.9)	4 (3.4)	7 (7.9)
ALANINE AMINOTRANSFERASE INCREASED	0 (0.0)	29 (7.1)	22 (20.4)	56 (8.7)	5 (4.2)	4 (4.5)
WEIGHT INCREASED	0 (0.0)	3 (0.7)	12 (11.1)	17 (2.6)	6 (5.1)	1 (1.1)
WHITE BLOOD CELL COUNT DECREASED	0 (0.0)	1 (0.2)	5 (4.6)	6 (0.9)	6 (5.1)	0 (0.0)
WEIGHT DECREASED	2 (8.0)	0 (0.0)	1 (0.9)	3 (0.5)	9 (7.6)	0 (0.0)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**5 (20.0)**	**115 (28.3)**	**21 (19.4)**	**157 (24.5)**	**36 (30.5)**	**14 (15.7)**
ARTHRALGIA	2 (8.0)	76 (18.7)	14 (13.0)	101 (15.7)	9 (7.6)	7 (7.9)
BACK PAIN	3 (12.0)	66 (16.2)	12 (11.1)	90 (14.0)	29 (24.6)	9 (10.1)
PAIN IN EXTREMITY	0 (0.0)	23 (5.7)	2 (1.9)	29 (4.5)	8 (6.8)	3 (3.4)
NERVOUS SYSTEM DISORDERS	**0 (0.0)**	**129 (31.7)**	**17 (15.7)**	**156 (24.3)**	**38 (32.2)**	**9 (10.1)**
HEADACHE	0 (0.0)	129 (31.7)	17 (15.7)	156 (24.3)	38 (32.2)	9 (10.1)
RENAL AND URINARY DISORDERS	**0 (0.0)**	**94 (23.1)**	**0 (0.0)**	**94 (14.6)**	**0 (0.0)**	**0 (0.0)**
CHROMATURIA	0 (0.0)	94 (23.1)	0 (0.0)	94 (14.6)	0 (0.0)	0 (0.0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	**0 (0.0)**	**12 (2.9)**	**3 (2.8)**	**15 (2.3)**	**7 (5.9)**	**0 (0.0)**
DYSMENORRHOEA	0 (0.0)	12 (2.9)	3 (2.8)	15 (2.3)	7 (5.9)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**2 (8.0)**	**148 (36.4)**	**5 (4.6)**	**164 (25.5)**	**34 (28.8)**	**7 (7.9)**
COUGH	0 (0.0)	117 (28.7)	4 (3.7)	129 (20.1)	25 (21.2)	6 (6.7)
OROPHARYNGEAL PAIN	2 (8.0)	83 (20.4)	1 (0.9)	89 (13.9)	18 (15.3)	2 (2.2)

1) On-Treatment Adverse Events are coded with MedDRA Dictionary Version 13.0
2) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group. The table is filtered for any MedDRA PT with >5% in the Ferriprox all doses or DFO columns. %Body System is calculated by the number of unique patients with PTs that appear on the report.
3) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
4) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in Ferriprox (all doses)
5) Data cutoff date: 31 Aug 2010

Major Safety Results

Deaths: In ApoPharma sponsored clinical studies, 17 deaths occurred, representing 1.3 deaths per 100 subject-years of exposure. Fourteen (14) of these deaths occurred in LA-04/06B, the compassionate use program. Subjects enrolled in that trial had failed other chelator therapy and many exhibited iron-induced toxicity prior to commencing treatment with deferiprone. Underlying diseases included thalassemia (9 subjects), myelodysplasia (3), myelofibrosis (2) thalassemia/hemoglobin E (1), Aase syndrome (1) and hereditary hemochromatosis (1). The reported causes of death were trauma (2 subjects), iron-induced cardiac disease (8), multi-organ failure (1), malignant lung tumor (1), acute myeloid leukemia (1), diarrhea (1), pleural effusion (1), adenocarcinoma (1) and intestinal obstruction (1). Only one of the deaths was considered to be possibly due to deferiprone use. These data are shown in the following table.

Table 6.1-1: Listing of Reported Deaths in Pooled Clinical Studies

Study ID	Subject ID	Treatment Group	Sponsor Defined Primary Diagnosis	Age at the time of Death (years)	Gender	Total Days on Study (before Death)	Days while Exposed	Days after end of Exposure (before Death)	Relationship to Study Drug	Primary Cause of Death (Preferred Term)*
LA_01	61	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	27	M	172	170	2	DOUBTFUL	CARDIAC FAILURE CONGESTIVE
LA_0206	604	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	22	M	1726	1706	20	NOT RELATED	INTERNAL INJURY
LA_04	38	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	23	F	53	46	7	DOUBTFUL	CARDIAC FAILURE CHRONIC
LA_04	39	FERRIPROX 75 MG/KG/DAY	MYELOFIBROSIS	68	M	209	180	29	NOT RELATED	MULTI-ORGAN FAILURE
LA_04	49	FERRIPROX 75 MG/KG/DAY	THALASSEMIA MAJOR	45	M	2704	2681	23	NOT RELATED	POST PROCEDURAL COMPLICATION
LA_04	98	FERRIPROX 91.2 MG/KG/DAY	THALASSEMIA MAJOR	53	F	2626	2606	20	NOT RELATED	ADENOCARCINOMA
LA_04	109	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	39	M	157	157	0	NOT RELATED	CARDIOMYOPATHY
LA_04	114	FERRIPROX 75 MG/KG/DAY	MYELOFIBROSIS	46	F	242	242	0	NOT RELATED	CARDIAC FAILURE
LA_04	127	FERRIPROX 75 MG/KG/DAY	MYELODYSPLASIA	65	F	410	302	108	NOT RELATED	LUNG NEOPLASM MALIGNANT
LA_04	172	FERRIPROX 75 MG/KG/DAY AND DFO	TRANSFUSION DEPENDENT AASE SYNDROME	20	M	27	26	1	NOT RELATED	CARDIAC FAILURE
LA_04	207	FERRIPROX 75 MG/KG/DAY	MYELODYSPLASIA	74	M	260	257	3	NOT RELATED	ACUTE MYELOID LEUKAEMIA
LA_04	220	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	18	M	30	29	1	NOT RELATED	CARDIAC FAILURE CONGESTIVE

LA_04	224	FERRIPROX 100 MG/KG/DAY	MYELODYSPLASIA	72	M	753	713	40	NOT RELATED	PLEURAL EFFUSION
LA_04	240*	FERRIPROX 96 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	31	M	2	2	0	NOT RELATED	ARRHYTHMIA AND CARDIAC FAILURE
LA_04	277	FERRIPROX 75 MG/KG/DAY AND DFO	THALASSEMIA MAJOR	32	F	6	5	1	POSSIBLE	CARDIOGENIC SHOCK
LA_11	107	FERRIPROX 50 MG/KG/DAY	HEMOGLOBIN E-THALASSEMIA DISEASE	33	M	148	146	2	DOUBTFUL	DIARRHOEA
LA_04	222	FERRIPROX 75 MG/KG/DAY	HEREDITARY HEMOCHROMATOSIS	53	F	343	343	0	NOT RELATED	INTESTINAL OBSTRUCTION

1) There are a total of 642 subjects systemic iron overload exposed to Ferriprox in Clinical Trials.

2) Subjects LA_04_41 (Cause=Hepatic Cirrhosis) and LA_04_199 (Cause=Unknown) died post-study withdrawal and are not included above as this information is not part of the Clinical Database.

3) Treatment Group is based on maximum dose taken. *Coded with MedDRA Dictionary Version 13.0

4) Age at the time of Death is calculated as (Date of Death or Withdrawal - Date of Birth)/365.25, rounded down to the nearest integer.

5) Relationship to study drug based on reporter's causality assessment.

6) *Subject LA_04_240 on Alternate/Combination Therapy with Ferriprox died from arrhythmia and cardiac failure 2 days after being exposed to Deferiprone. The Arrythmia and cardiac failure were pre-treatment (with Ferriprox) events. This withdrawal is included as an SAE.

6) Data cutoff date: 31 AUG 2010

In post-marketing surveillance, the sponsor has received reports of 19 deaths since the first marketing authorization in 1999. The causes of death included agranulocytosis due to deferiprone (13 patients), cardiac failure (4), fungal infection (1) and sepsis (1). These data are shown in the following table.

Table 6.2-1: Listing of Death reports fromPostmarketing surveillance of Ferriprox

Case ID	Age	Gender	Description of Reported Reaction	Reported Cause of Death	MedDRA Primary Preferred Term
2003AP000129	60	M	Agranulocytosis	Shock Septic	Agranulocytosis
2003AP000464	-	M	Agranulocytosis	Infection	Agranulocytosis
2003AP000465	83	F	Agranulocytosis	Sepsis	Agranulocytosis
2005AP000076	22	F	Agranulocytosis	Septic shock	Agranulocytosis
2005AP000519	20	F	Agranulocytosis	Septic shock	Agranulocytosis
2005AP001015	40	M	Agranulocytosis	Cerebral haemorrhage	Agranulocytosis
2005AP001024	34	F	Agranulocytosis	Sepsis	Agranulocytosis
2006AP000007	17	F	Agranulocytosis	Septic shock	Agranulocytosis
2006AP000139*	28	M	Severe cardiac illness	Cardiac arrhythmias	Cardiac failure
2006AP000205	40	M	Agranulocytosis	Multi-organ failure	Agranulocytosis
2006AP000252	71	F	Agranulocytosis	Sepsis	Agranulocytosis
2006AP000322	10	F	Agranulocytosis	Embolism lung	Pulmonary embolism
2007AP000425		F	Septicemia	Sepsis	Sepsis
2007AP000992	32	M	Heart failure	Cardiac failure congestive	Cardiac failure
2007AP001306	19	F	Agranulocytosis	Sepsis	Agranulocytosis
2008AP000847	12	F	Agranulocytosis	Septicaemia	Agranulocytosis
2008AP001566	40	M	Congestive heart failure	Cardiac failure congestive	Cardiac failure
2008AP003436		F	Heart failure	Cardiac failure	Cardiac failure
2009AP004595	71	F	Fungal infection	Fungal infection	Fungal infection

* Case 2006AP000139 was not included in the ISS due to the doubtful causal relationship to Ferriprox. However, since this case was initially submitted to the Agency as possibly related it is included in this update. The narrative for this case is presented in section 6.3.2.

The sponsor states that the new safety data reviewed in this submission do not alter the benefit/risk assessment of deferiprone.

Reviewer Comments. Deaths in the clinical trials appear to have generally been unrelated to the administration of deferiprone and were usually due to disease progression, co-morbid conditions or were unrelated. There were no deaths due to hepatic dysfunction. Most of the deaths in post-marketing reports were due to agranulocytosis, the last of which was reported in 2008. The absence of reports of death due to agranulocytosis subsequent to 2008 is believed by the sponsor to be the result of a vigorous risk management program of education of patients/physicians, the performance of weekly blood counts with immediate termination of the drug at the earliest development of neutropenia or agranulocytosis and aggressive supportive therapy when agranulocytosis is first recognized.

A review of the clinical summaries submitted by the sponsor indicates that all of the deaths were likely related to progression of the primary disease or to co-morbid conditions except for the following patient:

- 2009AP004924. A 53 year old patient with thalassemia who was treated with deferiprone from May, 1995 until November, 2009 was diagnosed with

adenocarcinoma in the liver (believed to be metastatic). Various stains of the tumor were considered not typical for hepatocellular carcinoma but that possibility could not be excluded. There was no comment in the report regarding the presence of cirrhosis or the degree of iron deposition. The question of a primary carcinoma of the liver was not resolved.

Serious Adverse Events: There were 231 serious adverse reactions reported in 147/642 subjects (22.9%) treated with deferiprone in pooled clinical studies. These data are shown in the following table.

Table 4.3-1: Summary of On-Treatment Serious Adverse Events by SOC in Pooled Clinical Studies

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
SUBJECTS WITH ANY SAE	**3 (12.0)**	**110 (27.0)**	**11 (10.2)**	**147 (22.9)**	**4 (3.4)**	**22 (24.7)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	**0 (0.0)**	**45 (11.1)**	**8 (7.4)**	**57 (8.9)**	**1 (0.8)**	**4 (4.5)**
NEUTROPENIA	0 (0.0)	28 (6.9)	7 (6.5)	39 (6.1)	1 (0.8)	4 (4.5)
AGRANULOCYTOSIS	0 (0.0)	9 (2.2)	2 (1.9)	11 (1.7)	0 (0.0)	0 (0.0)
LYMPHADENITIS	0 (0.0)	6 (1.5)	0 (0.0)	6 (0.9)	0 (0.0)	0 (0.0)
THROMBOCYTOPENIA	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
LYMPHADENOPATHY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CARDIAC DISORDERS	**0 (0.0)**	**8 (2.0)**	**0 (0.0)**	**17 (2.6)**	**1 (0.8)**	**9 (10.1)**
CARDIAC FAILURE CONGESTIVE	0 (0.0)	3 (0.7)	0 (0.0)	7 (1.1)	1 (0.8)	4 (4.5)
ATRIAL FIBRILLATION	0 (0.0)	1 (0.2)	0 (0.0)	4 (0.6)	0 (0.0)	3 (3.4)
CARDIAC FAILURE	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)	2 (2.2)
ATRIAL FLUTTER	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	1 (1.1)
ANGINA UNSTABLE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CARDIAC FAILURE CHRONIC	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CARDIOGENIC SHOCK	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
COR PULMONALE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INTRACARDIAC THROMBUS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
TORSADE DE POINTES	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
EAR AND LABYRINTH DISORDERS	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**2 (0.3)**	**0 (0.0)**	**1 (1.1)**
DEAFNESS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
VERTIGO	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
GASTROINTESTINAL DISORDERS	**1 (4.0)**	**7 (1.7)**	**0 (0.0)**	**8 (1.2)**	**0 (0.0)**	**0 (0.0)**
ABDOMINAL PAIN	0 (0.0)	4 (1.0)	0 (0.0)	4 (0.6)	0 (0.0)	0 (0.0)
ABDOMINAL ADHESIONS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
COLITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
DIARRHOEA	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PANCREATITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	**0 (0.0)**	**4 (1.0)**	**0 (0.0)**	**9 (1.4)**	**0 (0.0)**	**4 (4.5)**
PYREXIA	0 (0.0)	2 (0.5)	0 (0.0)	7 (1.1)	0 (0.0)	4 (4.5)
MULTI-ORGAN FAILURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PAIN	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
HEPATOBILIARY DISORDERS	**0 (0.0)**	**3 (0.7)**	**0 (0.0)**	**3 (0.5)**	**0 (0.0)**	**0 (0.0)**
CHOLELITHIASIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
HEPATIC CONGESTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
HEPATITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INFECTIONS AND INFESTATIONS	**0 (0.0)**	**21 (5.2)**	**2 (1.9)**	**34 (5.3)**	**0 (0.0)**	**10 (11.2)**
CELLULITIS	0 (0.0)	1 (0.2)	0 (0.0)	5 (0.8)	0 (0.0)	3 (3.4)
GASTROINTESTINAL INFECTION	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
INFECTIOUS MONONUCLEOSIS	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
SEPSIS	0 (0.0)	2 (0.5)	0 (0.0)	3 (0.5)	0 (0.0)	1 (1.1)
DEVICE RELATED INFECTION	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (2.2)
DEVICE RELATED SEPSIS	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (2.2)
PHARYNGOTONSILLITIS	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
PNEUMONIA	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
URINARY TRACT INFECTION	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
ACUTE SINUSITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
BACTERAEMIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
BACTERIAL INFECTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
BACTERIAL SEPSIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
BRONCHOPNEUMONIA	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CORNEAL ABSCESS	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
CYTOMEGALOVIRUS HEPATITIS	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
GASTROENTERITIS VIRAL	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INFLUENZA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
MENINGITIS BACTERIAL	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PYELONEPHRITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
SERRATIA SEPSIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
SINUSITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
STAPHYLOCOCCAL INFECTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
TONSILLITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
UPPER RESPIRATORY TRACT INFECTION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
VIRAL INFECTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
YERSINIA INFECTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	**1 (4.0)**	**11 (2.7)**	**0 (0.0)**	**12 (1.9)**	**0 (0.0)**	**0 (0.0)**
FEMUR FRACTURE	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
ROAD TRAFFIC ACCIDENT	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
TRANSFUSION REACTION	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
FEMORAL NECK FRACTURE	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
FOOT FRACTURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
FRACTURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
HIP FRACTURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INTERNAL INJURY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
STERNAL FRACTURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
THORACIC VERTEBRAL FRACTURE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INVESTIGATIONS	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**	**4 (0.6)**	**0 (0.0)**	**2 (2.2)**
ARTHROSCOPY	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
BLOOD GLUCOSE INCREASED	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.3)	0 (0.0)	2 (2.2)
METABOLISM AND NUTRITION DISORDERS	**0 (0.0)**	**4 (1.0)**	**0 (0.0)**	**9 (1.4)**	**0 (0.0)**	**5 (5.6)**
DIABETIC KETOACIDOSIS	0 (0.0)	1 (0.2)	0 (0.0)	3 (0.5)	0 (0.0)	2 (2.2)
DIABETES MELLITUS	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
HYPOGLYCAEMIA	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	1 (1.1)
DEHYDRATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
HYPOCALCAEMIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
HYPOKALAEMIA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**	**6 (0.9)**	**0 (0.0)**	**3 (3.4)**
BACK PAIN	0 (0.0)	1 (0.2)	0 (0.0)	2 (0.3)	0 (0.0)	1 (1.1)
BURSITIS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
INTERVERTEBRAL DISC PROTRUSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
JOINT EFFUSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
MUSCULOSKELETAL PAIN	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	**0 (0.0)**	**3 (0.7)**	**0 (0.0)**	**4 (0.6)**	**0 (0.0)**	**0 (0.0)**
ACUTE MYELOID LEUKAEMIA	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
ADENOCARCINOMA	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
LEUKAEMIA	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
LUNG NEOPLASM MALIGNANT	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
NERVOUS SYSTEM DISORDERS	**0 (0.0)**	**1 (0.2)**	**0 (0.0)**	**1 (0.2)**	**1 (0.8)**	**0 (0.0)**
ENCEPHALITIS	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
MIGRAINE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
PSYCHIATRIC DISORDERS	**0 (0.0)**	**2 (0.5)**	**0 (0.0)**	**4 (0.6)**	**0 (0.0)**	**2 (2.2)**
CONFUSIONAL STATE	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
MAJOR DEPRESSION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
OPPOSITIONAL DEFIANT DISORDER	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
SELF INJURIOUS BEHAVIOUR	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
SUICIDAL IDEATION	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)

Body System Preferred Term	FERRIPROX 50 mg/kg/d n=25 (%)	FERRIPROX 75 mg/kg/d n=407 (%)	FERRIPROX 100 mg/kg/d n=108 (%)	FERRIPROX (all doses) mg/kg/d n=642 (%)	DFO 50 mg/kg/d n=118 (%)	Alternate/Combination Therapy with FERRIPROX n=89 (%)
RENAL AND URINARY DISORDERS	**1 (4.0)**	**2 (0.5)**	**0 (0.0)**	**3 (0.5)**	**1 (0.8)**	**0 (0.0)**
RENAL COLIC	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)
NEPHROLITHIASIS	1 (4.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PYELOCALIECTASIS	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	**0 (0.0)**	**2 (0.5)**	**1 (0.9)**	**5 (0.8)**	**0 (0.0)**	**2 (2.2)**
CHYLOTHORAX	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
PLEURAL EFFUSION	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.2)	0 (0.0)	0 (0.0)
PULMONARY CONGESTION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
PULMONARY OEDEMA	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
RESPIRATORY DISTRESS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
SURGICAL AND MEDICAL PROCEDURES	**0 (0.0)**	**19 (4.7)**	**0 (0.0)**	**21 (3.3)**	**0 (0.0)**	**1 (1.1)**
SPLENECTOMY	0 (0.0)	8 (2.0)	0 (0.0)	8 (1.2)	0 (0.0)	0 (0.0)
CHOLECYSTECTOMY	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
KNEE OPERATION	0 (0.0)	3 (0.7)	0 (0.0)	3 (0.5)	0 (0.0)	0 (0.0)
ADENOTONSILLECTOMY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
CATHETERISATION VENOUS	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (1.1)
HERNIA REPAIR	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
LITHOTRIPSY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
MENISCUS OPERATION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
NAIL OPERATION	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
TYMPANOPLASTY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
URETEROLITHOTOMY	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
URETHRAL REPAIR	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)

1) On-Treatment Serious Adverse Events are coded with MedDRA Dictionary Version 13.0
2) This table is based on the primary Serious Adverse Event.
3) Percentage is calculated based on the number of subjects exposed with systemic iron overload primary diagnoses in each dosing group.
4) Subjects exposed to more than one Ferriprox dose are classified by their maximum dose.
5) There are 13 subjects whose maximum dose of Ferriprox is other than 50, 75 or 100, not exceeding 100 mg/kg/day. These Subjects are included in Ferriprox (all doses), where applicable.
6) Data cutoff date: 31 AUG 2010

For 60 of the SAEs, this led to discontinuation of deferiprone, and for 15 of the SAEs, the outcome was fatal. Seventy-eight of the SAEs were reported since the previous cut-off date of August 31, 2006. Of the 78, there were 15 episodes of neutropenia, 4 of agranulocytosis and 3 of pyrexia. Most of the other SAEs were reported in only a single patient and did not appear to be causally related to deferiprone. Sixty-one of the 78 SAEs were experienced by 27 subjects treated in study LA-04/06B (Compassionate Use Program) in which patients who could not be adequately treated with other chelators were eligible to obtain deferiprone. Many of these patients had organ damage from iron overload or had co-morbid conditions. The most common SAE in the clinical trials was neutropenia, occurring in 79/642 (12.3%) of patients.

Agranulocytosis was the most clinically important SAE, and occurred in 1.7% of patients (11/642) in clinical trials. Agranulocytosis was less common in patients with thalassemia (1.3%, 8/607 subjects) than it was in patients with non-thalassemic anemias requiring transfusion (8.6%, 3/35 subjects), including 2 with MDS and 1 with sickle cell disease.

The time of onset of agranulocytosis was 65 days to 9.2 years (median, 161 days) after commencing deferiprone therapy. The duration of agranulocytosis varied from 3 to 85 days (median, 10 days) but was longer in patients with non-thalassemic disorders (median, 19 days) compared to those with thalassemia (median, 9 days). There were no patients who had persistent agranulocytosis. Eight patients were treated with G-CSF. Three of the patients had developed neutropenia prior to agranulocytosis. These data are shown in the following table.

Table 4.3-2: Agranulocytosis episodes during Pooled Clinical Studies

Definition	Thalassemia	Other Systemic Iron Overload Conditions	Total
No. of Events	8	3	11
No. of Patients	8	3	11
Total No. of Patients with systemic iron overload	607	35	642
% of Patients	1.3	8.6	1.7
Total Exposure (pt yrs)	1286.3	52.5	1338.8
Rate (Patients)/100 pt-yrs	0.6	5.7	0.8
Rate (Events)/100 pt-yrs	0.6	5.7	0.8
Median Age (yrs) of Patients with Agranulocytosis	10	58	11
Age (Min / Max) yrs of Patients with Agranulocytosis	4 / 18	12 / 64	4 / 64
Sex of Patients with Agranulocytosis - Male / Female	2 / 6	1 / 2	3 / 8
Median Duration of DFP Exposure for Patients with Agranulocytosis (days)	157	302	181
Range of Duration of DFP Exposure for Patients with Agranulocytosis (days)	67 / 3329	181 / 2854	67 / 3329
Median Duration (days)	9	19	10
Duration (Min / Max) days	3 / 18	16 / 85	3 / 85
Median Time to Agranulocytosis (days)	160.5	301	161
Time to Agranulocytosis (Min / Max) days	65 / 3352	140 / 567	65 / 3352
G-CSF use in Agranulocytosis Events - Yes / No / Unknown	6 / 2 / 0	2 / 1 / 0	8 / 3 / 0
Hepatitis C of Agranulocytosis Patients - Yes / No / Unknown	2 / 6 / 0	0 / 3 / 0	2 / 9 / 0
Splenectomy of Agranulocytosis Patients - Yes / No / Unknown	1 / 5 / 2	1 / 2 / 0	2 / 7 / 2

Footnote:
1) Clinical Studies included: LA-01, LA-02/06, LA-03, LA-04/06B, LA08-9701, LA10-9902, LA-11, LA-15, LA16-0102, LA28-CMP, LA30-0307.
2) Patients exposed to ApoPharma's DFP with systemic iron overload primary diagnoses are included. Planned doses for these studies range from 45 to 100 mg/kg/day.
3) Years of Exposure = ((End Date of Exposure - First Date of Exposure +1) - sum of interruption days)/365.25
4) Age is calculated as (First Exposure Date - Date of Birth)/365.25, rounded down to the nearest integer
5) Duration of event (days) is calculated as (Date of AE Resolution - Date of AE Onset +1), where available.
6) Time to Event is calculated as (Date of AE Onset - First Date of Exposure).
7) Median Duration of DFP Exposure for Patients with Agranulocytosis (days) calculates the years of exposure for patients with agranulocytosis.
8) Hepatitis C positive-reports did not provide information if the positivity for Hepatitis C refers to the presence of antibodies or the presence of the Hepatitis C virus.
9) GCSF=Granulocyte Colony Stimulating Factor
10) Data cut off date: 31AUG2010.

SAEs experienced in clinical trials and believed to be related to deferiprone included neutropenia (38 subjects, 5.9%), agranulocytosis (11 subjects, 1.7%), torsade de pointes

(1 subject, 0.2%), deafness (1, 0.2%), hepatitis (1, 0.2%), cytomegalovirus hepatitis (1, 0.2%), serratia sepsis (1, 0.2%) and the need for arthroscopy (1, 0.2%).

SAEs reported in post-marketing experience that were not seen in the clinical trials include: hypersensitivity (2 cases), arthralgia (2 cases), polyarthritis (2 cases), cerebellar syndrome (2 cases), intracranial pressure increased (2 cases), and one case each of congenital anomaly, diplopia, retinal toxicity, gastric ulcer, vomiting, asthenia, chills, fungal infection, hepatitis infections, subcutaneous abscess, blood bilirubin increased, aspartate aminotransferase increased, metabolic acidosis, arthritis, bone pain, muscular weakness, myositis, altered state of consciousness, convulsion, headache, pyramidal tract syndrome, Henoch-Schoenlein purpura, and urticaria. In the post marketing experience there have been 94 SAEs of agranulocytosis and 96 SAEs of neutropenia.

Reviewer Comments. The clinically most important adverse reaction associated with the use of deferiprone is the development of agranulocytosis. This adverse reaction occurred in 1.7% of patients treated with the drug in clinical trials. It appears to be more common in patients with non-thalassemic disorders than in patients with thalassemia, perhaps because in the latter there is often a deficiency of bone marrow production and these patients may be more susceptible to an additional marrow insult caused by deferiprone. The development of neutropenia may be a herald of progression to agranulocytosis, but this is not clear. In patients who survive the episode of agranulocytosis, thus far no apparent permanent bone marrow incapacitation has been observed. No deaths due to agranulocytosis have been reported in clinical trials, but there have been 13 reported deaths due to agranulocytosis in post-marketing pharmacovigilance. The mechanism of the production of agranulocytosis has not been established.

Other adverse reactions associated with the use of deferiprone include gastrointestinal symptoms, arthropathy, thrombocytopenia, and fever. A single case of torsade de pointes has also been reported.

Laboratory Findings: The following analytes were assessed and re-integrated with updated information:

- Alanine aminotransferase (ALT). The following tables provide the numbers of subjects with normal values for ALT at baseline whose ALT increased to > 2 x ULN for 2 or more consecutive visits or were at those levels at the last on-treatment visit during the administration of deferiprone.

Table 7.1-2: Summary of Subjects in Pooled Clinical Studies with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN for two or more consecutive visits.

ALT > 2 x ULN n (%)		ALT > 3 x ULN n (%)		ALT > 5 x ULN n (%)	
FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)
41 (12.31)	2 (2.74)	21 (6.31)	1 (1.37)	6 (1.80)	0 (0.00)

1) Analysis was done on subjects with normal ALT at baseline

2) Percentage is calculated based on the number of subjects with normal ALT at baseline

ALT = Alanine Transaminase; FERRIPROX = Deferiprone; DFO = Deferoxamine; NA = Not Applicable; ULN = Upper Limit of Normal Reference Range

Cut-off Date: 31AUG2010

Table 7.1-3: Summary of Subjects in Pooled Clinical Studies with ALT values within the normal range at baseline, but greater than 2, 3 or 5 times the ULN at the last on-treatment visit.

ALT > 2 x ULN n (%)		ALT > 3 x ULN n (%)		ALT > 5 x ULN n (%)	
FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)	FERRIPROX (n = 333)	DFO (n = 73)
23 (6.91)	3 (4.11)	10 (3.00)	0 (0.00)	1 (0.30)	0 (0.00)

1) Analysis was done on subjects with normal ALT at baseline

2) Percentage is calculated based on the number of subjects with normal ALT at baseline

ALT = Alanine Transaminase; FERRIPROX = Deferiprone; DFO = Deferoxamine; NA = Not Applicable; ULN = Upper Limit of Normal Reference Range

Cut-off Date: 31AUG2010

- Serum creatinine. Deferiprone had no clinically important effect on serum creatinine values.
- Serum zinc. After re-integration, approximately 12% of subjects who had a normal serum zinc level at baseline showed a decrease in serum zinc to below the reference range. The clinical significance of this finding is not known.
- Absolute neutrophil counts (ANC). Clinical study LA30-0307 assessed the frequency and significance of the development of ANC between 1.0 – 1.5 x 10^9/L in patients receiving deferiprone. Six of 100 subjects met this categorization. Of these, 4 had a single episode that resolved despite continued deferiprone use. One had two episodes that resolved despite continued use. One had two episodes, after which agranulocytosis developed.

Reviewer Comments. The re-integration of laboratory data from recent safety data does not provide new insights into the types and frequencies of the adverse reactions that are associated with the use of deferiprone.

Summary of Safety Update

There do not appear to be any changes in the safety profile of deferiprone on the basis of the data provided in the updated safety review. The main difference in safety evaluation as compared to the review of safety in the original NDA submission is that there is now more safety experience in children because of the results from Study LA30-0307, which assessed the efficacy and safety of the use of an oral solution of deferiprone (100 mg/mL) in children.

The evaluation of safety is based on almost 25 years of human use of deferiprone, including 12 years of post-marketing surveillance. During that time, it is estimated that

there has been more than 35,000 person-years of use, in some cases exceeding more than a decade in a single individual.

The most important adverse reaction to the use of deferiprone is the development of agranulocytosis. This occurred in 1.7% of patients enrolled in the clinical trials submitted by the sponsor. Agranulocytosis occurred in 8/607 (1.3%) of patients with thalassemia and in 3/35 (8.6%) of patients with other types of anemia requiring transfusion and leading to hemosiderosis (2 with MDS and 1 with sickle cell disease). Three of these patients had developed neutropenia that was followed by agranulocytosis despite the discontinuation of the drug. The median time of onset was 161 days (range of 65 days to 9.2 years) after starting deferiprone therapy. The median duration of agranulocytosis was 10 days (range of 3 to 85 days). The mechanism has not been identified but appears to be via a suppressive effect on myelopoiesis. It appears to be an idiosyncratic reaction rather than a dose dependent effect, usually occurs within the first year of therapy but can occur even several years after commencing therapy. There were no deaths associated with the development of agranulocytosis in clinical trials and the agranulocytosis was reversible in all such patients. However, there have been 13 deaths due to agranulocytosis in post-marketing experience. There have been no deaths due to agranulocytosis reported since 2008, after the sponsor established an educational and observational program to alert patients and physicians to monitor blood counts weekly and to discontinue the use of deferiprone at the earliest indication of the development of neutropenia.

There were 57 serious adverse events in 642 persons (8.9%) treated with deferiprone in the clinical trials. Forty nine (49) of these were related to either agranulocytosis (11) or neutropenia (38). Thrombocytopenia occurred in 2 patients. There were single serious events of atrial fibrillation, cardiogenic shock, torsade de pointes, deafness, cytomegalovirus hepatitis, serratia sepsis and arthroscopy. Of 234 serious adverse events from post-marketing reports, 96 were for neutropenia and 94 were for agranulocytosis. The remainder were for 1 or 2 events distributed over a broad variety of organ systems (with one report of an increased bilirubin and one for a raised aspartate aminotransferase). Of a total of 642 persons treated with various doses of deferiprone, 245 (38.2%) were withdrawn from treatment with deferiprone, 99 of whom (15.4%) were withdrawn for the occurrence of adverse events. The adverse events leading to discontinuation were similar to those known to be associated with deferiprone, but for some of the patients, discontinuation was due to progression of the underlying disease or death due to the underlying disease.

Other adverse reactions that occur in persons treated with deferiprone and that may be related to the drug and may possibly be dose related include neutropenia and an increase in ALT. Adverse reactions that appear not to be dose related are gastrointestinal symptoms (nausea, diarrhea, abdominal pain), arthralgia and headache.

APPENDIX A

Tabular Listing of All Clinical Studies

Study Identifier: Study Title [country(ies)]	Objective(s) of the study	Study design and type of control	Test product(s), Dosage regimens; Route of administration	Number of Subjects	Healthy subjects or diagnosis of patients	Duration of Treatment
LA16-0102: Randomized trial comparing the relative efficacy of deferiprone to that of deferoxamine in removing excess cardiac iron in thalassemia major patients [Greece, Italy]	Primary objective: To determine if Ferriprox® (deferiprone) exhibits superior efficacy in removing excess iron from the heart compared to Desferal® (deferoxamine), as reflected by MRI T2* assessments Secondary objective: To evaluate relative efficacy of Ferriprox® with respect to Desferal® as assessed by serum ferritin concentration and LIC	Multicenter, randomized, open-label, active controlled clinical trial	Test product: Ferriprox® 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d., first 4 weeks. • 28.3 mg/kg, p.o., t.i.d., subsequent 4 weeks. • 33.3 mg/kg, p.o., t.i.d., remainder of the trial. Comparator product: Desferal® • 50 mg/kg/day, s.c., up to 12 hours infusion, 5-7 days/week	61 dosed; 56 completed	• Thalassemia major • Ongoing chelation therapy with Desferal® for at least the past 5 years • Not exposed to Ferriprox® within the last 2 years if the patients have been exposed to Ferriprox® for ≤ 6 months • Abnormal heart MRI T2* > 8 ms and <220ms	12 months
LA12-9907: Retrospective assessment of heart failure and survival during iron chelation with deferiprone or deferoxamine in subjects with transfusiondependent ß-thalassemia [Italy]	Primary objective: Investigate incidence of cardiac disease and survival in patients treated with Ferriprox® compared to patients treated with deferoxamine Secondary objective: Evaluate progression of cardiac disease in patients treated with either Ferriprox® or deferoxamine	Open label, controlled, single center, parallel, longitudinal, retrospective assessment	Test product: Ferriprox® 500 mg film-coated tablets • 75 mg/kg/day, p.o., 7 days/week • The dose was adjusted to patient need within range from 35-100 mg/kg/day Comparator product: Deferoxamine • 20 to 60 mg/kg/day, s.c., 8-12 hours infusion, 4-7 days/week	168 screened; 129 completed (54 deferiprone; 75 deferoxamine)[#]	Transfusion dependent β-thalassemia • Treated for at least four years with Ferriprox® (deferiprone) or deferoxamine	5 years
LA08-9701: Safety and efficacy of alternating deferoxamine and deferiprone compared to deferoxamine alone in the treatment of iron overload in thalassemia patients [Italy, Greece]	Evaluate relative efficacy and safety of alternating use of Ferriprox® and Desferal® in comparison with current standard monotherapy, Desferal®	Randomized, open label, controlled, parallel clinical trial	Test product: Ferriprox® 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d., 5 days/week Desferal® for the combination arm • 20-60 mg/kg/day, s.c.,	59 dosed; 59 completed	Transfusion dependent thalassemia receiving chelation therapy with deferoxamine • Serum ferritin concentration between 1000 and 4000 µg/L.	12 months

			8-12 hours infusion, 2 days/week Comparator product: Desferal® • 20-60 mg/kg/day, s.c., 8-10 hour infusion, 5-7 days/week			
LA10-9902: Population monitoring cytogenetics study. An open label, single crossover design study to determine the clastogenic potential of deferiprone (L1) and compare that to the clastogenic potential of Desferal® (deferoxamine) in iron-overloaded, transfusion dependent individuals with thalassemia	To determine if there is significant change in the frequency of chromosomal aberrations in circulating lymphocytes in subjects receiving deferoxamine therapy following a switch to deferiprone; and to compare that frequency in subjects that switched from deferiprone to deferoxamine. To determine the frequency of chromosomal aberrations in circulating lymphocytes in subjects following long term therapy with deferiprone compared to long term deferoxamine therapy.	Single center, open label, Single treatment, Active controlled, Crossover design with no intervening drug-free period	Test product: Deferiprone (1st transfusion cycle) • 25 mg/kg, p.o., t.i.d., a period of at least 20 days Deferoxamine (evening of the 2nd transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, until day 20 of the transfusion cycle Comparator product: Deferoxamine (1st transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, a period of at least 20 days Deferiprone (evening of the 2nd transfusion cycle) • 25 mg/kg, p.o., t.i.d., until day 20 of the transfusion cycle	20 dosed; 20 completed	Patients with thalassemia major, who are regularly transfused with blood filtered by a blood bank, for white blood cells, • Receiving ongoing chelation therapy with deferoxamine or deferiprone for the past three months	A period of at least 20 days
LA-02: Trial of deferiprone in thalassemia	Primary objective: To determine incidence of agranulocytosis and other serious adverse events Secondary objective: To determine the efficacy of deferiprone in treatment of iron overload, as assessed by serum ferritin concentration	Prospective, multicentered, Open label, single treatment, uncontrolled clinical study	Test product: Deferiprone, 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	187 dosed; 162 completed	Patients 10 years or older with transfusion dependent β-thalassemia • Serum ferritin level above 2000 µg/L or a liver iron above 4.0 mg iron/g dry weight liver • Unable or unwilling to take deferoxamine	12 months
LA-02/06: Clinical study report for 4 years of therapy with Ferriprox™ in patients participating in studies LA-	**LA-02:** Primary objective: to determine incidence of agranulocytosis and other serious adverse events	Multicentered, open-label, uncontrolled maintenance study	Test product: Ferriprox® 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	LA-02 : 187 dosed; 162 completed;	**LA-02:** • Patients 10 years or older with transfusion dependent β- thalassemia • Serum ferritin level above 2000 µg/L	1 year under LA-02 and 3 years under

02/06 [U.S., Italy]	Secondary objective: to determine the efficacy of deferiprone in treatment of iron overload, as assessed by serum ferritin concentration **LA-06:** Primary objective: to monitor long-term safety and effectiveness of Ferriprox® in the same cohort of patients as LA-02			LA-06: 160 dosed; 84 completed	or a liver iron above 4.0 mg iron/g dry weight liver • Unable or unwilling to take deferoxamine **LA-06:** • Patients who have completed LA-02 and are willing to continue treatment with Ferriprox	LA-06 for a total of 4 years
LA-02/06: Clinical study report for 7 years of therapy with Ferriprox™ in patients participating in studies LA-02/06	**LA-02:** Primary objective: to determine incidence of agranulocytosis and other serious adverse events Secondary objective: to determine efficacy of deferiprone in treatment of iron overload, as assessed by serum ferritin concentration **LA-06:** Primary objective: to assess the occurrence of adverse events and long-term effectiveness of deferiprone in the same cohort of patients as LA-02 Secondary objective: To provide study medication to patients until licensure of product or cessation of clinical development	Multicentered, open-label, single treatment, uncontrolled maintenance study	Test product Ferriprox® 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	LA-02 : 187 dosed; 162 completed LA-06 (48 month interim Statistical Report): 160 dosed; 84 completed LA-06 (7 year Statistical Report): 160 dosed; 70[#] completed	LA-02 • Patients 10 years or older with transfusion dependent β- thalassemia • Serum ferritin level above 2000 µg/L or a liver iron above 4.0 mg iron/g dry weight liver • Unable or unwilling to take deferoxamine LA-06 • Patients who have completed LA-02 and are willing to continue treatment with Ferriprox	7 years
LA-01: Randomized trial of deferiprone (L1, Ferriprox®) and deferoxamine (DFO) in thalassemia major [Canada]	1. Comparison of the relative effectiveness of deferiprone and deferoxamine as reflected by the ability of each chelator to: a. achieve net negative iron balance b. reduce tissue stores of iron c. reduce body stores of iron 2. Comparison of the compliance with deferiprone and	Multicentered, open-label, randomized, parallel active controlled study	Test product: Deferiprone, 500 mg film coated tablets • 25 mg/kg, p.o., t.i.d. Comparator product: Deferoxamine • 50 mg/kg, s.c., up to 12 hours infusion, 4-7 times/week	71 dosed • 35 in deferiprone • 36 in deferoxamine 42 completed • 21 in deferiprone • 21 in deferoxamine	Patients 6 years and 10 months of age or older with β-thalassemia	2 years followed by a 1 year follow-up period

	deferoxamine 3. Testing of relative safety of deferiprone and deferoxamine 4. Comparison of the relative quality of life enjoyed by patients during administration of either chelator					
LA-03: The long term efficacy and safety of deferiprone in patients with transfusion dependent thalassemia (formerly compassionate use of deferiprone in thalassemia patients) [Canada]	Under compassionate use program: to collect clinical experience with the use of deferiprone therapy for the treatment of iron overload. Long-term primary objectives: to determine the longterm safety and efficacy of deferiprone	Single centre, open label study	Test product: Deferiprone • Until OCT 1993, the test product was manufactured at University of Toronto and encapsulated by Novopharm Inc., Canada. • No data regarding quality of this product is available to ApoPharma Inc. • 25 mg/kg, p.o., t.i.d. Deferiprone, 100 mg, 250 mg and 500 mg film-coated tablets • From OCT 1993, the test product was manufactured by Apotex Inc. • 25 mg/kg, p.o., t.i.d.	29 patients enrolled. 25 dosed with Apotex formulation. No data were available for other 4 Patients; 11[#] completed	Patients 10 years of age or older • Transfusion dependent thalassemia patients with iron overload • Unable to take currently available chelation therapy • Or had a history of serious noncompliance with currently licensed iron chelation therapy.	4 years (University of Toronto formulation) 3 years (Apotex Inc. formulation)
LA-04/06B: The compassionate use of deferiprone (L1) in patients with thalassemia [Canada, Italy, U.S.]	Primary objective: to provide treatment of chronic iron overload in patients with transfusion dependent anemia for whom deferoxamine is contraindicated or inadequate Secondary objective: to assess long-term safety and efficacy of Ferriprox® alone or in combination with deferoxamine for the treatment of chronic iron overload in patients with transfusion dependent anemia	Compassionate Use Program under LA-04 protocol. Ferriprox® was supplied in 3-month allotments for an approved patient until licensure of the product or until the patient is withdrawn from the program.	Test product: Ferriprox® 500 mg film-coated tablets • 25-33 mg/kg, p.o., t.i.d.	165[#] dosed, 23[#] completed	Patients with thalassemia • Patients with other chronic iron-overload conditions • Require iron chelation • Deferoxamine is contraindicated or Inadequate (unwilling, unable, allergy, toxicity, lack of effect, inability to comply with parenteral infusions, or unavailability of the drug).	Mean duration for all patients (N=86): • 1.3 (0-9.8) years. Mean duration for thalassemia Patients (N=58): • 1.2 (0-8.4) years Mean duration for patients with other chronic Transfusion dependent

						conditions (N=28): • 1.3 (0-9.8) Years
LA-11: Prevention of iron mediated oxidation of RBC and platelet membranes in β-thalassemia diseases by deferiprone (L1) [Thailand]	To determine the efficacy of Ferriprox for reducing the iron overload in Thai patients with β-thalassemia/hemoglobin E diseases To determine the safety of Ferriprox for the treatment of iron overload in Thai patients	Prospective, open-label, uncontrolled study	Test product: Ferriprox Mean dose 48.1±5.74 mg/kg, p.o., b.i.d. or t.i.d.	24 dosed; 16# completed	Thai patients with β-thalassemia/hemoglobin E disease	Mean time on therapy: 334±179 (5-536) days; 16 patients were treated for more than 1 year; 20 patients were treated for longer than 3 months
LA-15-0002: Prevention of iron mediated oxidation of RBC and platelet membranes in β-thalassemia diseases by deferiprone (L1)	Primary objective: To monitor the efficacy and safety of Ferriprox® for treatment of iron overload in subjects with transfusion dependent thalassemia in Iran	Single center, open label, single treatment, uncontrolled study.	Test product Ferriprox® • 25 mg/kg, p.o., t.i.d.	29 dosed; 26 completed	Subjects with transfusion - dependent β-thalassemia • Last serum ferritin value, assessed within the past 12 months, was found to be greater than 2500 mg/L.	3 months
Borgna-Pignatti et al. (Blood 2006): Cardiac morbidity and mortality in deferoxamine- or deferiprone-treated patients with thalassemia [Italy]	To compare the occurrence of cardiac disease and survival in patients treated only with deferoxamine (DFO) and in patients who had their therapy switched from DFP to deferiprone (DFP) during the study period.	Epidemiologic, observational study.	Test product: Deferiprone • 75 mg/kg/day, p.o., in 3 divided doses Comparator product: Deferoxamine • 50 mg/kg/day, s.c., 5-6 times/week	359 patients treated with deferoxamine only. 157 patients switched to deferiprone at one point during the study period	Patients with thalassemia major • Born between 1970 and 1993 • As of Jan 1995, were alive, had not had a cardiac event, received chelation therapy throughout study period and on follow-up, had not undergone bone marrow transplant	9 years
LA17-9701: The safety and effectiveness of deferiprone in a largescale, 3-year study in Italian patients.	To evaluate the longterm safety and efficacy of deferiprone	Open label, uncontrolled, active drug surveillance	Test product: Deferiprone • 75 mg/kg/day, p.o., in 3 divided doses	532 dosed. Treatment with deferiprone: • < 1 year, 13 patients • 1 to 2 years, 63 patients • 2 to 3 years, 167 patients • At least 3 years, 168 patients	Thalassemia major or intermediate • Serum ferritin > 2000µg/L, or liver LIC > 4 mg/g liver dry weight	Mean 2.27 years
LA10-9902: Population monitoring cytogenetics study. An open label, single crossover design study to determine the clastogenic potential of	To determine if there is significant change in the frequency of chromosomal aberrations in circulating lymphocytes in subjects	Single center, open label, single treatment, active	Test product: Deferiprone (1st transfusion cycle) • 25 mg/kg, p.o., t.i.d., a period of at least 20	20 dosed; 20 completed	Patients with thalassemia major, who are regularly transfused with blood filtered by a blood bank, for white blood cells, • Receiving ongoing chelation therapy	A period of at least 20 days

deferiprone (L1) and compare that to the clastogenic potential of Desferal® (deferoxamine) in iron-overloaded, transfusion dependent individuals with thalassemia	receiving deferoxamine therapy following a switch to deferiprone; and to compare that frequency in subjects that switched from deferiprone to deferoxamine. To determine the frequency of Chromosomal aberrations in Circulating lymphocytes in subjects following long term therapy with deferiprone compared to long term deferoxamine therapy.	controlled, crossover design with no intervening drug-free period	days Deferoxamine (evening of the 2nd transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, until day 20 of the transfusion cycle Comparator product: Deferoxamine (1st transfusion cycle) • 20-60 mg/kg/day, s.c., 4-7 days/week, a period of at least 20 days Deferiprone (evening of the 2nd transfusion cycle) • 25 mg/kg, p.o., t.i.d., until day 20 of the transfusion cycle		with deferoxamine or deferiprone for the past three months	
LA-02: Trial of deferiprone in thalassemia	Primary objective: To determine incidence of agranulocytosis and other serious adverse events Secondary objective: To determine the efficacy of deferiprone in treatment of ironoverload, as assessed by serum ferritin concentration	Prospective, multicentered, Open-label, single treatment, uncontrolled clinical study	Test product: Deferiprone, 500 mg film-coated tablets • 25 mg/kg, p.o., t.i.d.	187 dosed; 162 completed	Patients 10 years or older with transfusion dependent β-thalassemia • Serum ferritin level above 2000 µg/L or a liver iron above 4.0 mg iron/g dry weight liver • Unable or unwilling to take deferoxamine	12 months
LA28-CMP[@]: The compassionate use/named patient program of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anemias [Egypt, Malaysia, Singapore]	Primary objective: To provide treatment with Ferriprox oral solution to iron-overloaded pediatric patients with transfusion-dependent anemias for whom deferoxamine is contraindicated or inadequate	Multi-center, open label, single treatment, uncontrolled, compassionate use/named patient basis program		83 dosed; 62 completed (72 patients previously enrolled in LA30-0307)		
LA30-0307[@]: 24-week, open label, uncontrolled study of the safety and efficacy of Ferriprox oral solution in iron-overloaded pediatric patients with transfusion-dependent anemias [Egypt, Indonesia, Malaysia]	Primary objective: To assess the safety of Ferriprox oral solution for the treatment of iron overload in pediatric patients with transfusion-dependent anemias	Open label, uncontrolled		100 dosed; 95 completed		

[#]number completed updated in 4/13/11 submission; [@]two studies in pediatric patients; not previously reported

Table based on information in sponsor's table in section 5.2 in 1/29/2009 submission and sponsor's Table 5.1-1 in 4/13/2011 submission